IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Simon J. Oh
Art Unit	:	1615
Applicant	:	Richard W. Voellmy
Serial No.	:	09/939,161
Filed	:	August 24, 2001
For	:	Compositions and Methods Relating to Prevention of Chemotherapy-Induced Alopecia

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF RICHARD W. VOELLMY, Ph.D., Esq. UNDER 37 C.F.R. §1.132

Sir:

I, Richard W. Voellmy, Ph.D., of Pully, Switzerland, hereby declare:

THAT, my *curriculum vitae* is attached hereto as Exhibit A;

THAT, I am the named inventor on the above-referenced patent application (hereinafter referred to as "the patent application");

THAT, through my years of research, I have kept up to date on the technical literature and maintained contact with experts in the field by participating in professional meetings and seminars, and by direct personal contact. As a result, I am familiar with the general level of skill of those working in the fields of chemotherapy induced alopecia (hair loss);

THAT, I have read and understood the specification and claims of the patent application, the Office Actions dated February 26, 2003, August 12, 2003, May 6, 2004, October 5, 2004, October 7, 2005, and the references cited in the foregoing Office Actions;

AND, being thus duly qualified, do further declare:

1. The Office Action has rejected claims 26-33 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. In articulating the grounds of rejection, the Office Action argues that "[i]n methods of treating a condition, a time-dependence factor must be taken into account and that this factor cannot be easily predicted". The Office Action also argues that insufficient guidance and direction is provided to allow one skilled in the art to practice the claimed invention without undue experimentation. Finally, the Office Action argues that the specification fails to enable the claimed invention because there are no working examples and that one skilled in the art "would be burdened with undue 'painstaking experimentation study'" to practice the claimed invention.

2. While I do not agree that the specification fails to enable the claimed invention, I provide the following evidence demonstrating the effectiveness of the claimed invention in preventing hair loss (alopecia) in an animal model typically used for such studies using the methodologies described within the specification.

3. As described in the specification, animal models have been described in the literature that are suitable for such studies (see as-filed specification at page 21, line 10 through line 24). Rat/mouse models for the study of chemotherapy induced alopecia are useful because the animals demonstrate a follicular anagen phase that is comparable to humans (100% vs. 90%); the animals are responsive to chemotherapies alopecic in humans; the animals produce highly visible and definitive results; and the animals allow for the possibility to assess the chemotherapeutic effect of an agent on malignant cells introduced into the animal (see Appendix B, page 1).

4. Animals were treated as discussed in the specification (see, page 19, line 28 through page 21, line 8 and/or page 28, lines 25-32). For the experiment described herein, animals were randomized into groups and localized heat treatment was provided to one group 7 hours prior to chemotherapy. Localized heat treatment comprised contacting the scalp of the animals with a device that transferred heat (temperatures of about 39°C to about 45°C; specification at page 20, lines 15-

17) to a specific point on the animal's head for a period of time that ranged from about 15 minutes to about 120 minutes (specification at page 20, lines 15-17). VP16 (or etoposide; a chemotherapeutic agent) was injected intraperitoneally 2.5 μg/g. A second dose of chemotherapeutic agent was provided 24 hours later. Alopecia was recorded 7 days after initiation of chemotherapy. The experiments were then repeated. As demonstrated in Appendix B, page 2, localized heat treatment 7 hours prior to treatment with VP16 prevented alopecia at the site contacted with heat. Additional experiments were conducted with other chemotherapeutic agents with similar results (see Appendix B, page 3). As illustrated therein, chemotherapy-induced alopecia was reduced or prevented in animals treated with taxol (paclitaxel), cyclophosphamide, etoposide, and a combination of cyclophosphamide/adriamycin. Taxol was administered subcutaneously as no non-lethal dose could be found for intraperitoneal administration.

5. Animals were also assessed for the induction of heat shock protein as a result of treatment with heat. Animals were treated as described in the preceding paragraph and tissue samples were assayed for the induction of a heat shock protein response. Briefly, one day after heat treatment, skin sections from the nape of the neck of about 9-day old heat-treated Sprague-Dawley rats were taken from the heat-treated area or from the same area of the neck of non-heat treated animals. Skin sections were embedded in paraffin blocks and incubated with polyclonal mouse Hsp70 (5 μL/mL) for 1 hour. Sections were then incubated for 30 minutes with biotinylated anti-mouse IgG and sections were further incubated with avidinated peroxidase for 30 minutes. Slides were exposed to DAB and H_2O_2 and counterstained with hematoxylin. As illustrated on page 4 of Appendix B, administration of heat to the animals resulted in the induction of a heat shock protein response that was associated with protection against chemotherapy-induced alopecia. Non-heat-treated animals showed little induction of heat shock protein.

6. Localized application of physical or chemical inducers do not appear to protect malignant/cancerous cells from chemotherapeutic agents. As illustrated in Appendix B, pages 5-7, the tumor cell line MIA C51 was administered intraperitoneally to animals. The animals were then

subjected to localized heat treatment followed by the administration of a chemotherapeutic agent (cyclophosphamide). As indicated at page 5 of Appendix B, malignant cells were not protected by localized application of heat to the animals. All animals that did not receive cyclophosphamide died within about 29 days after injection of the tumor cell line. The administration of cyclophosphamide to animals injected with the cancer cell line resulted in a decrease of the mortality rate. Thus, the localized application of heat to the animals did not appear to impact the sensitivity of cancer cells to cyclophosphamide.

7. Accordingly, it is respectfully submitted that one skilled in the art, using the teachings of the as-filed specification, would be able to practice the invention as claimed without being subjected to undue experimentation.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed: Richard W. Voellmy
Richard W. Voellmy, Ph.D., Esq.

Date: March 6, 2006

EXHIBIT A

RICHARD VOELLMY

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Dept. of Biochemistry & Molecular Biology, University of Miami, 1011 N.W. 15 Street, Miami, FL 33136. Phone: (305) 243-5815. Facsimile: (305) 243-3064

Education

Swiss Federal Institute of Technology, ETH-Zuerich, Switzerland, 1967-71, Diploma in Microbiology and Biochemistry

University of Zuerich, Switzerland, 1971-3, studies in Economics

Swiss Federal Institute of Technology, ETH-Zuerich, Switzerland, 1971-5, Doctorate in Microbiology and Biochemistry (Dr. Natw.)

University of Miami, School of Law (Night Program), Miami, FL, 1991-4, Juris Doctor

Professional Experience

1971-5	Graduate studies, Dept. of Microbiology, Swiss Federal Institute of Technology, ETH-Zuerich, Switzerland
1975-8	Postdoctoral Fellow and (1978) Principal Research Associate, Dept. of Physiology, Harvard Medical School, Boston, MA
1978-82	Research Associate, Dept. of Molecular Biology, University of Geneva, Switzerland
1979	Visiting Assistant Professor of Physiology, Harvard Medical School, Boston, MA
1982-3	Assistant Professor, Dept. of Biochemistry, University of Miami, School of Medicine, Miami, FL
1982-8	Consultant to Battelle Memorial Institute, Geneva, Switzerland
1983-7	Associate Professor, Dept. of Biochemistry, University of Miami, School of Medicine, Miami, FL

1987-2004	Professor, Dept. of Biochemistry & Molecular Biology, University of Miami, School of Medicine, Miami, FL; Professor Emeritus since 2004.
1990	Co-Founder of StressGen Biotechnologies Corp., Victoria, B.C.
1995-1999	Vice-President for Planning and Intellectual Property, StressGen Biotechnologies Corp., & Member of its Scientific Advisory Board
1999-2000	Scientific Director, Debiopharm S.A., Lausanne, Switzerland
2000-present	Founder and Managing Director, HSF Pharmaceuticals S.A., Lausanne Switzerland
2005	Co-Founder of MedicalHeat S.A.

Professional Societies & Activities

American Society for Biochemistry & Molecular Biology
Florida Bar Association
Dade County Bar Association
U.S. Patent Bar
AIPLA
Editor, Cell Stress & Chaperones (-2003)
Guest Editor, Methods (2004)
Director, Ophthalmopharma A.G., Zuerich, Switzerland

Publications (abstracts omitted)

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U.S. patents and published patent applications, and PCT applications

US 6,342,596: Molecular regulatory circuits to achieve sustained activation of genes of interest by a single stress

US 5,646,010: Methods and compositions for expression of competent eukaryotic gene products

US 5,614,381: Method for the inducible production of proteins in genetically modified eukaryotic host cells multiplied in vivo

US 5,346,812: Teratogen assay

US 20050192219: Therapies involving mutated heat shock transcription factor

US 20050130306: Viral vectors whose replication and, optionally, passenger gene are controlled by a gene switch activated by heat in the presence or absence of a small molecule regulator

US 20030008349: Molecular regulatory circuits to achieve sustained activation of genes of interest by a single stress

US 20020001629: Compositions and methods relating to prevention of chemotherapy-induced alopecia

WO2005056806: Viral vectors controlled by a gene switch

WO2003020227: Compositions and methods relating to prevention of chemotherapy-induced alopecia

WO199957290: Molecular regulatory circuits to achieve sustained activation of genes of interest by a single stress

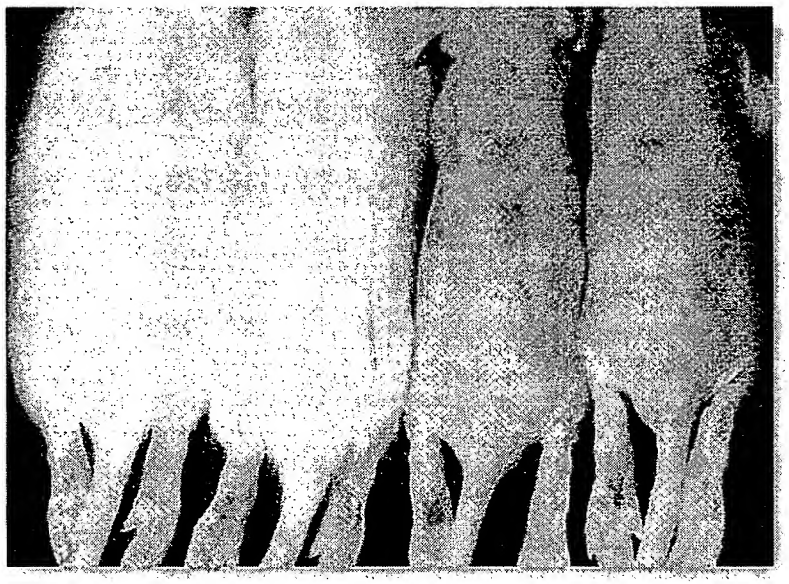
WO199831803: Therapies involving mutated heat shock transcription factor

WO198909822: Method for the in-vivo production and testing of proteins by recombinant gene expression in selected host cells

WO198705935: Methods and compositions for expression of competent eukaryotic gene products

EXHIBIT B

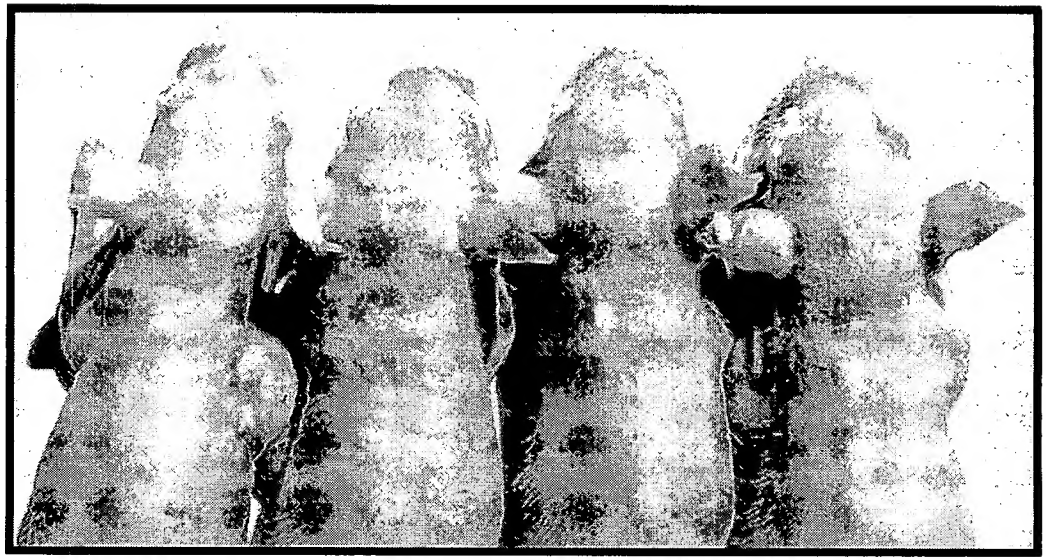
Advantages of the Rat Model:



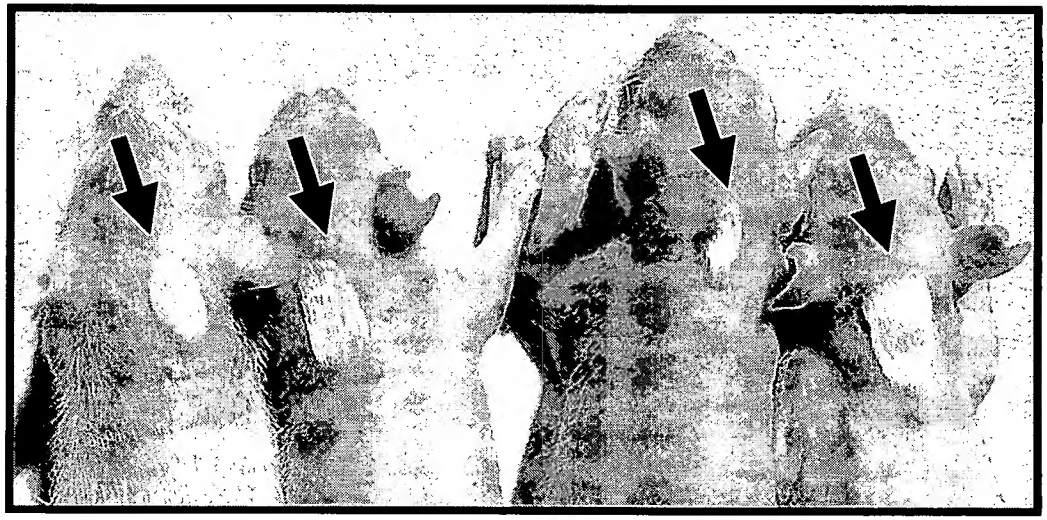
- Anagen phase comparable to humans (100% vs. 90%)
- Responsive to chemotherapies alopecic in humans
- Highly visible and definitive results
- Possibility to assess effect on malignant cells

Protection from VP16-Induced Alopecia

No heat pretreatment; i.p. chemotherapy with etoposide



Localized heat treatment 7 h prior to i.p. chemotherapy with etoposide

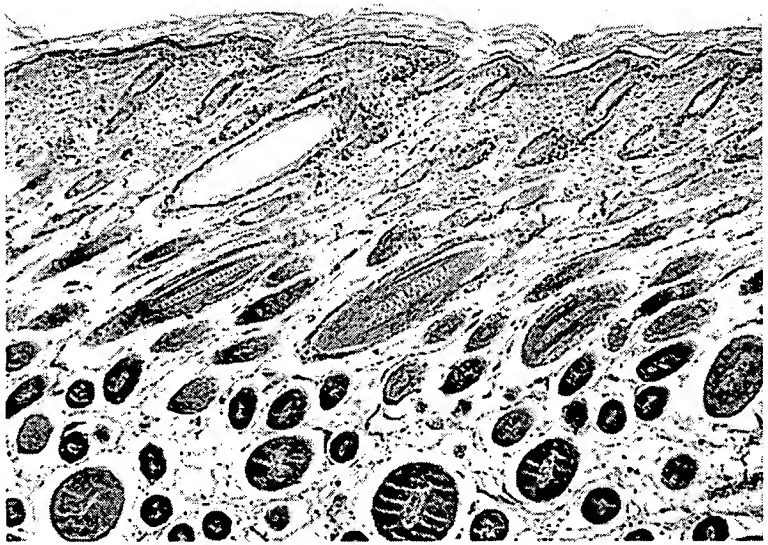


Localized protection at the site of heat application

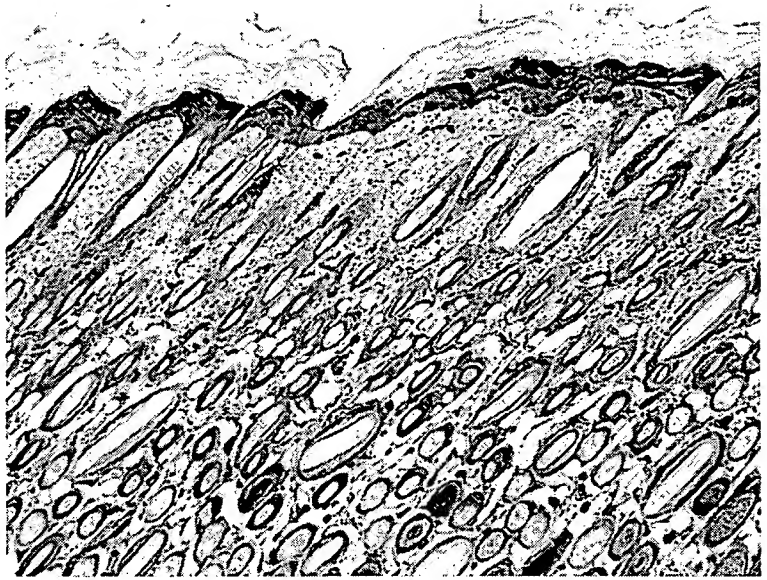
Protection against Major Classes of Chemotherapy-Inducing Drug Substances

Chemotherapy agent (s)	Range(s) of concentration(s)	Route of administration	No. animals w. patch of protected fur	No. animals exposed	Frequency of protective effect
Etoposide	2.5 μg/g, twice	intraperitoneal	45	48	94%
Cyclophosphamide	35.5 μg/g, once	intraperitoneal	29	30	97%
Cyclophosphamide/ Adriamycin	20-30 μg/g once/ 2.5-4.5 μg/g twice	intraperitoneal	56	56	100%
Taxol	5 μg/animal twice	subcutaneous	7	7	100%

Induction of Hsp70 in Hair Follicles



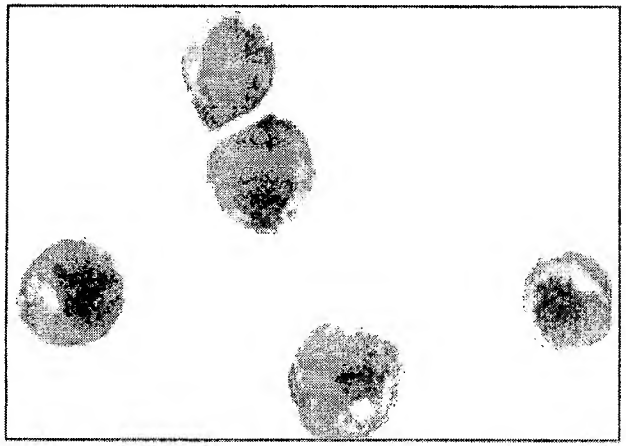
Unheated animal



Heat-treated animal

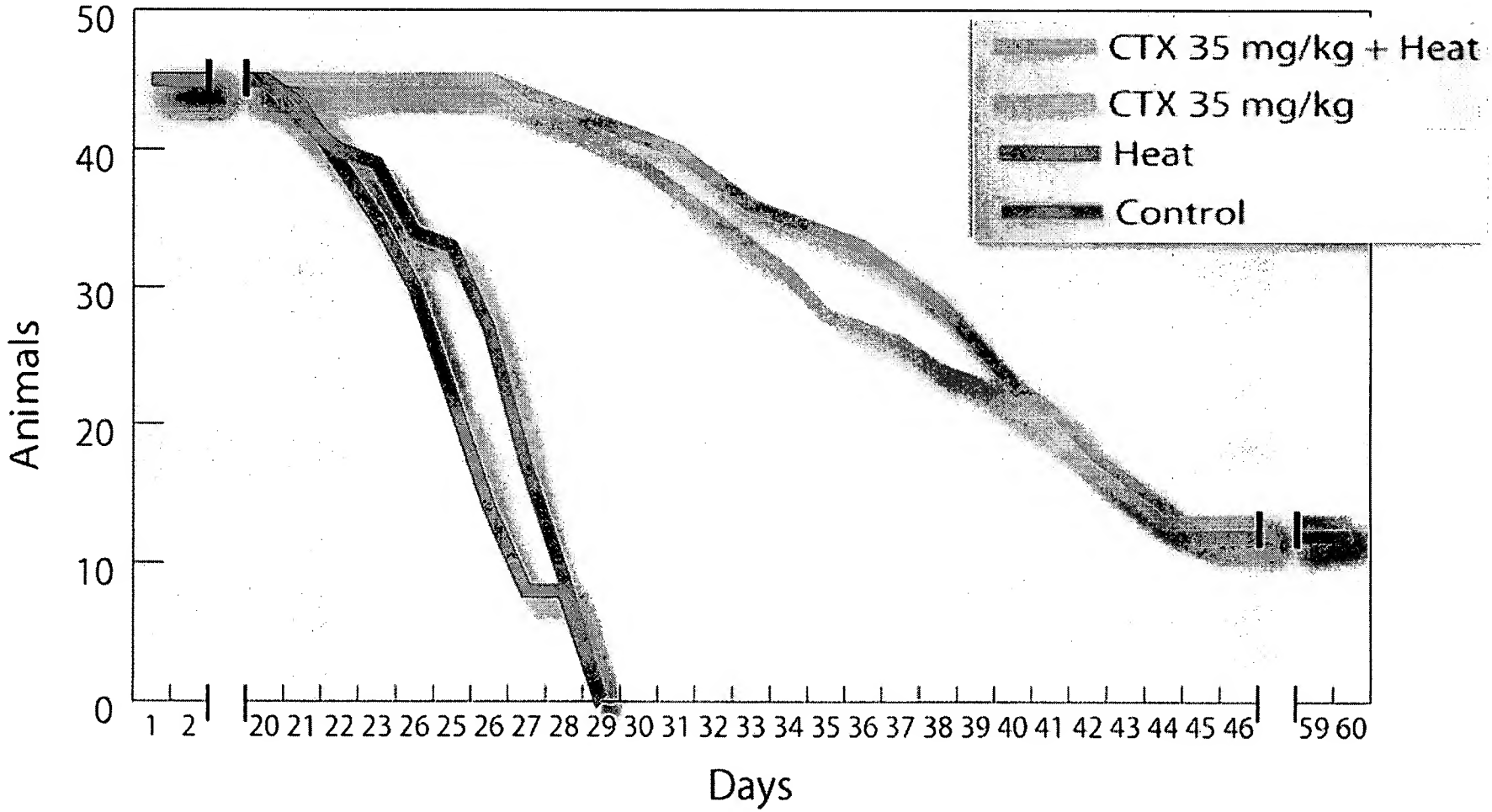
Skin sections from the nape of the neck of about 9-day old Sprague-Dawley rats. Sections were taken from the heat-treated area one day after heat treatment. Hsp70 immunostaining (brown; blue: counterstain)

Transplanted Chloroleukemia Model



- Four groups of 8-day old rats (n=45) received an i.p. injection of tumor cell line MIA C51 ($1x10^5$ cells)
- Six hours later, animals received localized heat treatment
- Cyclophophamide (35mg/kg) was administered 24 hours later

Effect of Localized Heat on Survival Outcome



Conclusions

- Localized application of physical inducers are an effective method for preventing chemotherapy-induced alopecia
- Localized application of physical inducers in vivo do not protect malignant cells from chemotherapy